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Prior regular exercise reverses the decreased effects of sleep deprivation on brain-derived neurotrophic factor levels in the hippocampus of ovariectomized female rats

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ABSTRACT

Previous studies indicated that brain-derived neurotrophic factor (BDNF) is the main candidate to mediate the beneficial effects of exercise on cognitive function in sleep deprived male rats. In addition, our previous findings demonstrate that female rats are more vulnerable to the deleterious effects of sleep deprivation on cognitive performance and synaptic plasticity.

Therefore, the current study was designed to investigate the effects of treadmill exercise and/or sleep deprivation (SD) on the levels of BDNF mRNA and protein in the hippocampus of female rats.

Intact and ovariectomized (OVX) female Wistar rats were used in the present experiment. The exercise protocol was four weeks treadmill running and sleep deprivation was accomplished using the multiple platform method. Quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) and immunoblot analysis were used to evaluate the level of BDNF mRNA and protein in the rat hippocampus respectively.

Our results showed that protein and mRNA expression of BDNF was significantly ($p < 0.05$) decreased after 72 h SD in OVX rats in compared with other groups. Furthermore, sleep deprived OVX rats under exercise conditions had a significant ($p < 0.05$) up-regulation of the BDNF protein and mRNA in the hippocampus.

These findings suggest that regular exercise can exert a protective effect against hippocampus-related functions and impairments induced by sleep deprivation probably by inducing BDNF expression.

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1. Introduction

Human and animal studies suggest that sleep has an important role in certain types of learning and memory and neuronal plasticity [1]. Accordingly, sleep deprivation causes memory deficit and decreases hippocampal level of BDNF [2,3]. In addition, BDNF is present in high concentration in the hippocampus and cerebral cortex and is very important for learning and memory [4].

Sleep disorders are almost frequent in modern society particularly in menopausal women. In menopausal women, sleep disturbances may be the most important indications for hormone therapy and certainly necessitate to be used as specific treatment in this group [5,6]. Additionally, despite the beneficial effects of estrogen on the brain functions, hormone replacement therapy increased adverse cardiovascular and oncological effects [7]; there is noticeable attention in developing healthier therapeutic approaches to alleviate sleep deprivation-associated impairments.

It has been indicated that exercise is one of the most potent non-pharmacological interference that can improve the cognitive functions around the postmenopausal period [8].

It has been demonstrated that exercise can alter some neurotransmitters and neurotrophin expression [4]. Altered expression of neurotrophic factors, for example BDNF is recognized to play a vital role in the hippocampus-related functions, synaptic plasticity [9,10] and psychiatric disorder [11]. Furthermore, it has been indicated that regular exercise can modulate the induction of mRNA and protein of BDNF within the hippocampus which may contribute to the maintenance of brain health and synaptic plasticity [4,12,13].

Several lines of evidence indicate that BDNF is a potential mediator of the central effects of estrogen. In particular, there are the extensive similarities between the functions of estrogen and BDNF in the CNS [14]. BDNF also provides both neurotrophic and neuroprotective support to different subpopulations of neurons, and is mostly associated

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with both learning and memory processes within the hippocampus [4,15,16]. It is possible that such properties may enhance specific learning and memory processes and help to reduce cognitive impairment associated sleep loss [17] and neurodegenerative disease [18,19].

Results from previous studies revealed that 24 h SD negatively affects cognitive function of rats by suppressing related signaling cascade such as BDNF in the hippocampus and such impairments can be prevented by regular exercise [17,20]. Interestingly, we have previously showed that female rats are more susceptible to the impairing effects of 72 h SD on spatial learning and memory in the Morris water maze task [21].

The aim of the current study was to examine the effects of regular exercise and/or SD on the level of BDNF protein and mRNA in the hippocampus of female rats.

2. Material and methods

2.1. Animals

Female Wistar rats (weighing 200–250 g) were used in the present study. Animals were caged in groups of four with access to food and water ad libitum. The rats were housed under a 12-h light–dark schedule (lights on: 07:00–19:00 h) and standard conditions of temperature (23 ± 1 °C). Two groups of intact and ovariectomized (OVX) rats were randomly chosen as the following subgroups: control (stayed in home cages), SD, exercised and exercised plus SD group. All procedures were performed in compliance with the National Research Council's Guide for the Care and Use of Laboratory Animals and approved by the Ethics Committee of Kerman Neuroscience Research Center (Ethics Code: KNRC-92-33).

2.2. Surgical procedures

All of the operations were carried out under general anesthesia using a mixture of ketamine (60 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.). Both ovaries were removed by a small mid-abdominal incision under aseptic situations. After ovariectomy, all of the rats were kept in a controlled animal room for one month [22].

2.3. Treadmill exercise

Rats ran as forced exercise for five day per week (from Saturday to Wednesday at 0° inclination) for four weeks during the light cycle, between 9:00 and 14:30 (they received a mild shock, 0.25 mA, when they stopped running). The rats were allowed to habituate to treadmill environment for 30 min during 2 successive days before the beginning of the exercise protocol to minimize nonspecific stress responses. The exercise protocol used in the current experiment was mild-moderate in that it gradually increased in velocity and time across the 4 week period. The exercise procedure included the following stages: 30 min for the first two weeks (at 10 m/min speed), 45 min for the third week and 60 min for the fourth week (both at 15 m/min speed). Every 15 min during each session, the animals had a five minute rest period [17].

2.4. Induction of sleep deprivation

Columns-in-water method (multiple platforms method) was used to induce SD. This apparatus (90 cm × 50 cm × 50 cm) contained 10 columns (10 cm high, 7 cm diameter located 2 cm above the water level) which were designed in two rows and spaced 10 cm apart (edge to edge). The apparatus permits rats to move from one platform to another. The animal was placed on top of a small platform. As a result, SD was achieved when the animal began rapid eye movement sleep (REM), losing muscle tone causing the rats to contact the water and awaken.

During the study, the rats had free access to clean water bottles and food pellet baskets were always hanging from the top of the chamber. In the present research, SD was induced for 72 h as previously explained [21]. The cage mates (4 rats) were put together in a chamber to retain social stability and were kept under standard conditions [12:12-h light–dark cycle at a controlled temperature (23 ± 1 °C)] in the sleep deprivation period.

Sleep deprivation was accomplished for 24 h after performing the last exercise session in the exercise/SD groups.

2.5. Molecular experiments

For molecular experiments, animals were anesthetized with atmosphere CO_2 in desiccators jar with low pressure flow of CO_2 [23]. After decapitation, both whole hippocampi were rapidly separated on an ice-cold surface and frozen in liquid nitrogen. The dissected hippocampi from each rat were randomly distributed for further western blot and RT-PCR assays and stored at −80 until homogenization.

2.5.1. BDNF immunoblot analysis

Sample preparation for immunoblot analysis was performed as previously reported [24]. The dissected hippocampal tissues were homogenized in ice-cold buffer containing 10 mM Tris–HCl (pH 7.4), 1 mM EDTA, 0.1% SDS, 0.1% Sodium deoxycholate, 1% NP-40 with protease inhibitors (1 mM phenylmethylsulfonyl fluoride, 2.5 μg/ml of leupeptin, 10 μg/ml of aprotinin) and 1 mM sodium orthovanadate, using a tissue homogenizer (Silent Crusher S Homogenizer, Germany) at a medium speed for 5 s, repeated 3 to 5 times. The homogenate was centrifuged at 14,000 rpm for 15 min at 4 °C. Protein concentrations were determined using the Bradford protein assay (Bio-Rad Laboratories, Muenchen, Germany). An equal amount of protein (40 μg) was resolved electrophoretically on 12.5% SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to PVDF membranes (Hybond ECL, GE Healthcare Bio-Science Corp., NJ, USA). During electrophoresis, the molecular weight was monitored with a pre-stained protein ladder (Fermentas, Life Science). Membranes were blocked with 5% nonfat powdered milk in Tris-buffered saline-Tween 20 (TBS-T) (0.1% Tween 20 in 150 mM Tris–HCl, pH 7.5) for 1.5 h at room temperature and thereafter, the membranes were incubated overnight with a primary rabbit polyclonal antibody for BDNF (1:1000, sc-20981; Santa Cruz Biotechnology, Santa Cruz, USA,) at 4 °C. After washing in TBS-T buffer (three times for 5 min, at room temperature) the membranes were incubated for 2 h at room temperature with an anti-rabbit IgG secondary antibody conjugated with horseradish peroxidase (1:15,000; GE Healthcare Bio-Sciences). Both primary and secondary antibodies were diluted in blocking buffer. The antibody-antigen complexes were visualized using the ECL system (Amersham Biosciences) and then exposed to Lumi-Film chemiluminescent detection film (Roch, Germany). Lab Work analyzing software (UVP, UK) was used to analyze the intensity of the expression. To control for loading, the membranes were stripped and reassayed using an antibody for β-actin (Cell Signaling Technology Inc., Beverly, MA, USA; 1:1000).

2.5.2. Semi-quantitative PCR

Total hippocampal RNA was isolated using a modification of the guanidine isothiocyanate-phenol-chloroform method using RNX+ reagent [25]. The isolated RNA was eluted with 20 μl of RNase-free water. All RNA was quantitated by spectrophotometer (Eppendorf AG, Hamburg, Germany) and optical density (OD) 260/280 nm ratios were determined. If A260/280 of extracted RNA had a value of ~2.0, it was considered as pure RNA samples and recruited in the next experimental steps. In addition, the extracted RNA was electrophoresed (1.5% agarose gel) and stained with ethidium bromide. After visual assessment of the 28 s and 18 s of rRNA band, we considered intact or good RNA. The same concentration of extracted RNA was used to make cDNA. Briefly, the single-strand cDNA was synthesized from

purified total RNA using M-Mulv reverse transcriptase and oligo-dT primer. At first, cDNA concentration was measured by a spectrophotometer and the equal amount of cDNA was used in our PCR. A semi-quantitative PCR method was used [24]. Reaction was accomplished in a final volume of 50 μl containing 2 μg tissue cDNA, 1 μl of each BDNF sense and antisense primers, 2 μl dNTP mixture, 1.5 μl MgCl2, 5 μl 10× PCR Buffer, 0.3 μl Taq DNA polymerase, and 37.2 μl distillate water. Three separate PCR reactions were performed to study gene expression in the samples acquired from each rat. Each PCR reaction was accomplished using selective forward and reverse primers for BDNF and β-actin (as an internal standard) genes. Primer sequences used for PCR were as follows: BDNF-forward: 5′-GAC GAC GAC GTC CCT GGC TGA-3′, BDNF-reverse: 5′-ACG ACT GGG TAG TTC GGC ACT GG-3′; and β-actin-forward: 5′-CCC AGA GCA AGA GAG GCA TC-3′, β-actin-reverse: 5′-CTC AGG AGG AGC AAT GAT CT-3′. All sequences of primers were synthesized by Metabion International AG (Martinsried, Germany). Taq DNA polymerase (Roche, Germany) used for DNA amplification and reactions were set up according to the manufacturer's protocol. After denaturation at 95 °C for 5 min, PCR was performed by 25 cycles (45 s at 94 °C, 45 s at 60 °C and 45 s at 72 °C), followed by final extension for 3 min at 72 °C. The PCR products were subsequently analyzed on 1.5% agarose LMMP (Roche, Germany) gel and the obtained bands were quantified by a densitometric analysis (Lab Works analyzing software, UVP, UK).

2.6. Statistical analysis

Statistical analysis carried out using statistical package SPSS for window (version 16). All values were presented as means ± standard error of mean (SEM). All comparisons among the groups were also analyzed with two-way ANOVA followed by Tukey's post hoc multiple comparison test. The band density values were expressed as BDNF/β-actin ratio for each sample. The averages for different groups were compared using one-way ANOVA, followed by followed by Tukey test. $p < 0.05$ was considered significant.

3. Results

3.1. Protein and mRNA levels of BDNF

In our study, lowest levels of BDNF protein (0.78 ± 0.017) were detected in the hippocampus of sleep deprived rats as compared to control group (0.98 ± 0.047; $p = 0.012$) of OVX animals. Similarly, there was also a significant reduction ($p < 0.05$) in the levels of protein in the sleep-deprived OVX group compared to all other groups. In addition, the difference was statistically significant between the two sleep deprived intact and OVX groups (OVX = 0.78 ± 0.017, intact = 0.99 ± 0.032; $p = 0.012$) (Fig. 1). As indicated in Fig. 2, consistent with the observed changes in BDNF protein levels, a significant decrease in BDNF mRNA level (0.49 ± 0.019) was observed only in SD-OVX group in compared control (0.62 ± 0.022; $p = 0.001$) and other groups ($p < 0.05$). Furthermore, BDNF mRNA levels in the SD-OVX group were significantly lower than those in SD intact animals (OVX = 0.49 ± 0.019, intact = 0.60 ± 0.023; $p = 0.012$). However, exercised/SD rats showed significantly elevated levels of BDNF protein and mRNA as compared to sleep-deprived OVX rats (protein level: 1.04 ± 0.049 vs 0.78 ± 0.017, $p < 0.001$ and mRNA levels: 0.62 ± 0.02 vs 0.49 ± 0.019, $p = 0.001$) which was similar to those in control and exercise groups. Therefore, the significant down-regulation of the BDNF protein and mRNA in sleep deprived OVX female rats was prevented by regular treadmill exercise (Figs. 1 and 2 respectively).

4. Discussion

The most important objective of the experiments was to examine the effect of exercise and/or 72 h SD on protein and mRNA expression

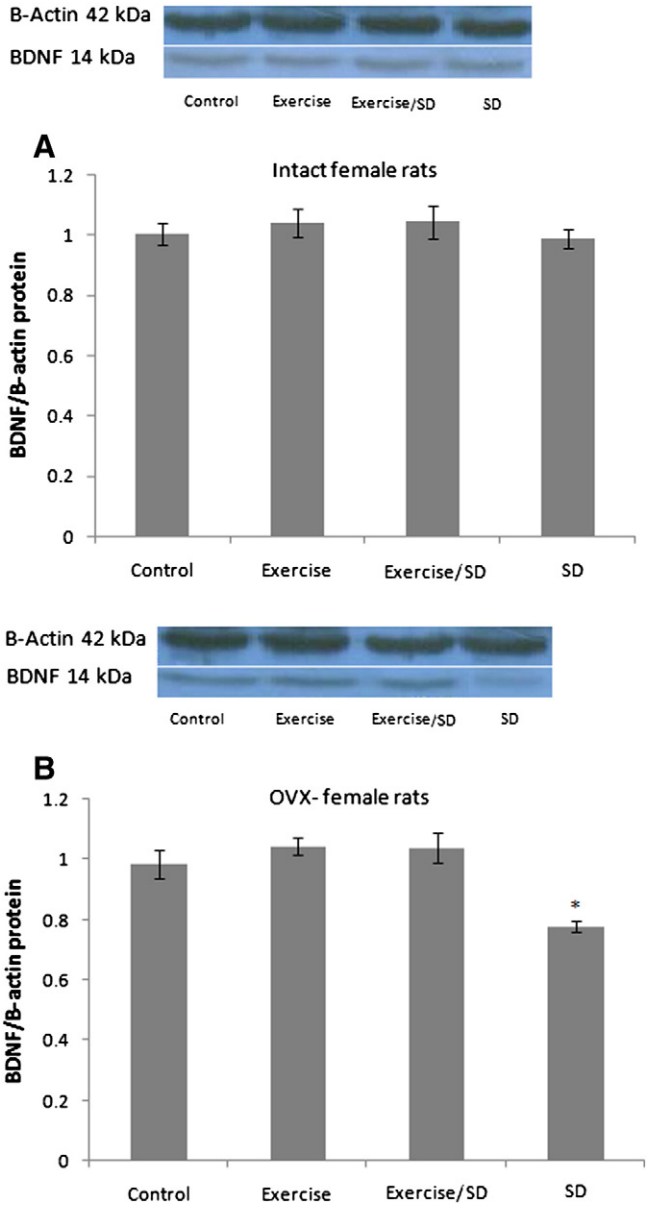

Fig. 1. Effect of regular exercise and/or 72 h sleep deprivation (SD) on the brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus of female rats. SD could decrease the BDNF protein levels only in the hippocampus of ovariectomized female rats. Meanwhile regular treadmill exercise improved these impairments. Each point in the graphs represents the mean ± S.E.M. (4–7rats/group). β-Actin was used as an internal control.*$p < (0.05–0.001)$ indicates significant difference from other groups.

of BDNF in the female rats. To test the potential protective effects of ovarian hormones against the SD-induced BDNF changes, we used ovariectomized female rats in this study. Data from our molecular assays showed that SD could decrease the BDNF protein and mRNA levels only in the hippocampus of OVX female rats. Meanwhile, regular treadmill exercise attenuated these impairments.

Our results also showed that SD could not decrease the hippocampal BDNF protein and mRNA of the intact female rats. In addition, OVX animals were more susceptible than intact animals to the negative effect of sleep loss on BDNF levels. Interestingly, in our previous study, we found that OVX female rats were more vulnerable to impaired effects of SD on spatial learning and memory than intact animals [21]. Electrophysiological results of our previous reports also indicated that SD caused impairment of hippocampal E-LTP in intact and OVX female rats. However, SD-OVX group displayed more deficits in LTP than intact female animals, but this difference was not significant

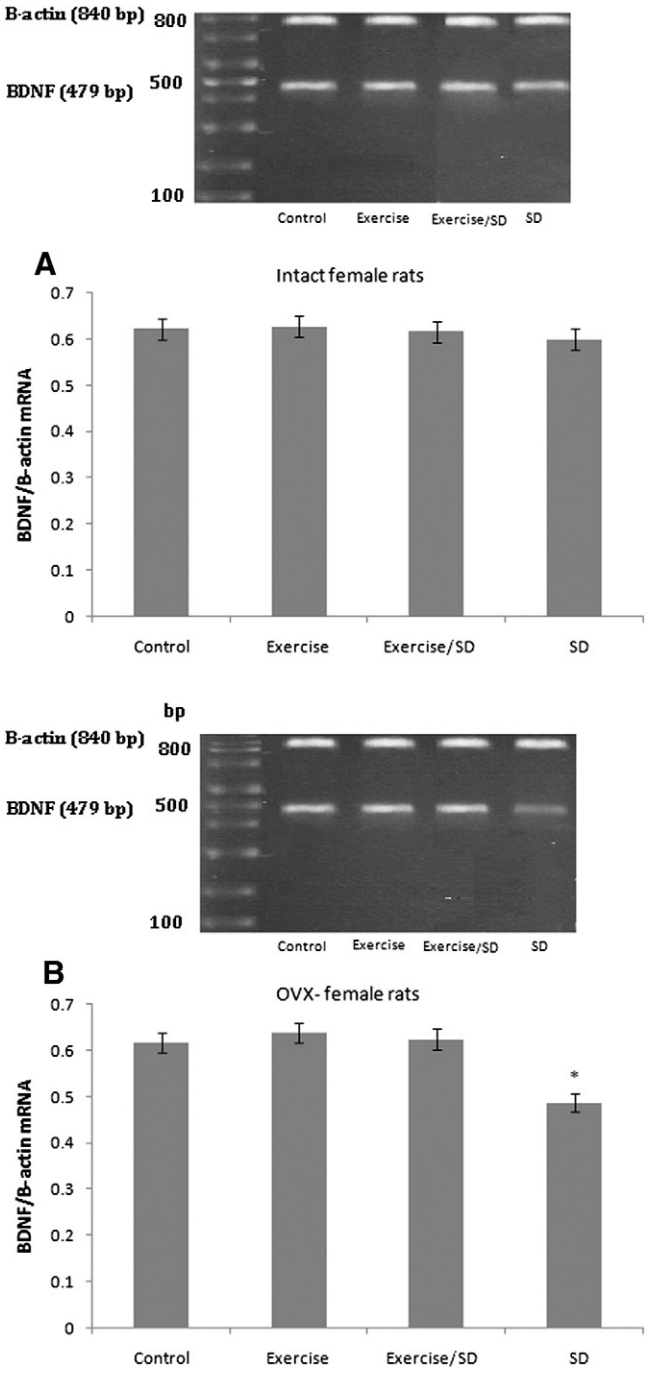

Fig. 2. Effect of regular exercise and/or 72 h sleep deprivation (SD) on the mRNA levels of brain-derived neurotrophic factor (BDNF) in the hippocampus of female rats. BDNF mRNA levels decreased only in the hippocampus of sleep deprived ovariectomized female rats. Therefore regular treadmill exercise attenuated this impairment. Each point in the graphs represents the mean ± S.E.M. (4–7rats/group). β-Actin was used as an internal control.*$p < (0.05–0.001)$ indicates significant difference from other groups.

[26]. It seems that depletion of endogenous sex steroid hormones is the main candidate for mediating the more sensitive OVX female rats to the adverse effects of sleep loss on hippocampus-related performance. As well as, it seems that sleep deprivation-induced changes in spatial learning and memory and synaptic plasticity correlate with changes in BDNF levels.

Several studies have reported the deleterious effects of sleep deprivation on cognitive performances and signaling molecules in the hippocampus of male rats [17,20] For instance, other molecular experiments have indicated that the expression of key signaling proteins and trophic factors such as, BDNF is impaired after sleep deprivation and sleep disorder in male animals [3,27–30]. Additionally, there are well-documented evidences for sex difference in many aspects of brain structure, learning and memory, neurotransmitter systems, and neuroendocrine regulation [31]. However, there are no further studies in this area to confirm or refute these observations in female rats.

It has been previously indicated that estrogens have some important benefits on the aging brain [32]. Postmenopausal estrogen replacement therapy can delay the decline in cognitive function [33] and reduces the risk of Alzheimer's disease [34]. Moreover, BDNF gene expression increases in response to estrogen [14]. Some studies have suggested that the level of estrogen may play an important role in the regulation of sleep [35]. The role of female sex steroids in sleep regulation is particularly obvious in postmenopausal women, who have low levels of circulating estrogen [35,36] and are more vulnerable to the deleterious effects of poor sleep on cognitive performance [21]. Although, human study indicated that differences in mood, sleep, and general health among premenopausal and menopausal women are not significant [37].

We used the platform method for the induction of sleep deprivation which depends on the loss of muscle tone during REM sleep. Although this technique can suppress about 95% of REM sleep, it can interfere with NREM sleep as well [38]. This technique also eliminates both the isolation and immobilization stress which accompanied with the other methods [39]. In addition, the previous study in our laboratory indicated that the differences of corticosterone levels and the performances in the Morris water test were not significant among the control, sham platform (wide platform) and SD groups [21]. It appeared that the cognitive deficit in sleep-deprived rats on the narrow platforms was mainly the result of sleep loss and not from stresses of the aquarium. Other findings are also consistent with our results [17,20,40].

However, in the current investigation we found that four weeks of regular exercise prevented the deleterious changes induced by SD on BDNF levels of hippocampus in OVX female rats. Other experiments, in agreement with our finding, have indicated that regular exercise prevents deleterious changes of signaling molecules such as BDNF in sleep deprived male animals [17,41].

It is well known that the preservation of BDNF might be crucial for the maintenance of neural plasticity and disease resistance during aging and in neurodegenerative situations [42]. Therefore, hippocampal BDNF can mediate the efficacy of exercise on cognitive functions [10].

It is demonstrated that BDNF mRNA expression is up-regulated by both estrogen and exercise [43]. It seems that the interaction among estrogen, physical exercise and hippocampal BDNF is probably to be a main point for the protection of brain health [43].

Although physical exercise could prevent the decreasing effect of SD in the OVX female rats, we did not observe any effect of treadmill running on BDNF mRNA and protein levels in the hippocampus of exercised groups of intact and ovariectomized animals. This is consistent with a recent report which showed the absence of changes in hippocampal BDNF levels in exercised animals [44]. These findings support the concept that maybe forced exercise regimens exert positive effects in the face of an insult or impairment such as sleep loss, ischemia, stroke or neurodegeneration.

However, some studies have shown that both voluntary and forced exercises can increase BDNF and other signaling molecules in the hippocampus [4,17].

These contradictory outcomes may be because of the differences in the length, type and intensity of the physical exercise used as well as the differences in age and strains of the experimental animals.

Studies on the role of BDNF in hippocampus-dependent learning and memory have produced conflicting findings. It is documented that BDNF has an important role in hippocampal-dependent learning and memory [45,46]. In contrast, other investigations showed that central administration of BDNF has no effect on the learning rate of the spatial learning-impaired rats [47]. Therefore, variation in methodologies, including the length and type of physical exercise and experimental

protocol might cause the different results. In addition, in the prior study, relative levels of BDNF protein were evaluated within specific hippocampal sublayers [17,41] whereas in the present experiment, BDNF levels were evaluated within the total hippocampus.

The limitation of the present study is extreme sleep deprivation (72 h), which might not be generalizable to humans. Therefore, further studies are also required to assess the effects of shorter sleep deprivation period or sleep restriction on BDNF level in female rats.

In conclusion, these findings suggest that regular exercise exerts a protective effect against hippocampus related functions and synaptic plasticity impairments induced by sleep deprivation probably by inducing BDNF protein and mRNA expression.

Conflict of interest

The authors declare that there are no conflicts of interest in our study.

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